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Current standard treatment of adult acute promyelocytic leukaemia

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Summary

The outcome of patients with acute promyelocytic leukaemia (APL) has dramatically improved over the last two decades, due to the introduction of combined all-*trans* retinoic acid (ATRA) and chemotherapy regimens and, more recently, to the advent of arsenic trioxide (ATO). ATRA and anthracycline-based chemotherapy remains a widely used strategy, providing cure rates above 80%, but it is associated with risk of severe infections and occurrence of secondary leukaemias. ATO is the most effective single agent in APL and, used alone or in combination with ATRA or ATRA and reduced-intensity chemotherapy, results in greater efficacy with considerably less haematological toxicity. The toxic profile of ATO includes frequent, but manageable, QTc prolongation and increase of liver enzymes. Two large randomized studies have shown that ATRA + ATO is superior to ATRA + chemotherapy for newly diagnosed low-risk APL resulting in 2–4 year event-free survival rates above 90% and very few relapses. According to *real world* data, the spectacular progress in APL outcomes reported in clinical trials has not been paralleled by a significant improvement in early death rates, this remains the most challenging issue for the final cure of the disease.

Keywords: acute promyelocytic leukaemia, PML/RARA, all-trans retinoic acid, arsenic trioxide.

Acute promyelocytic leukaemia (APL) is an infrequent form of acute myeloid leukaemia (AML) with specific biological and clinical features. These include a unique disease hallmark, the PML/RARA fusion protein underlying the t(15;17) chromosome translocation, a frequent and life-threatening coagulation disorder, and an exquisite sensitivity to anthracycline chemotherapy, all-*trans* retinoic acid (ATRA) and arsenic trioxide (ATO). Taken together, these features require a tailored approach to diagnosis and management (Wang & Chen, 2008; Sanz & Lo-Coco, 2011; de Thé *et al*, 2012).

The treatment of APL has been revolutionized in the past two decades by the advent of ATRA and ATO. Although these agents were initially used empirically and, unlike imatinib, were not designed in the laboratory as tailored treatments, ATRA and ATO were soon shown to target RARA and PML, respectively, i.e. the two distinct moieties of the disease-specific oncoprotein PML/RARA (de Thé *et al*, 2012). The use of variable combinations of ATRA, ATO and chemotherapy tested in several large trials worldwide, have transformed this hyper-acute, once rapidly fatal disease into the most highly curable acute leukaemia in adults, with long-term remission rates now exceeding 80% (Tallman, 2004; Adès *et al*, 2008; Sanz & Lo-Coco, 2011; Lo-Coco *et al*, 2013; Burnett *et al*, 2015; Iland *et al*, 2015). However, as shown by recent registry studies, early death still remains a major problem as many patients fail to be promptly diagnosed and/or receive appropriate treatment in time (Lehmann *et al*, 2011; Park *et al*, 2011; McClellan *et al*, 2012; Paulson *et al*, 2014).

Recently, two large randomized trials have compared the standard ATRA plus chemotherapy approach *versus* ATRA-ATO combinations, showing significantly improved outcomes and considerably less haematological toxicity in patients receiving the chemotherapy-free approach (Lo-Coco *et al*, 2013; Burnett *et al*, 2015). As a result, modern guidelines now indicate ATRA-ATO as the first recommended choice for patients with non-high risk disease [defined as those with presenting white blood cell (WBC) count $<10 \times 10^9$/l]. As for high-risk patients, the same ATRA-ATO strategy combined with reduced-intensity anthracycline or anthracycline-like chemotherapy (e.g. gemtuzumab ozogamicin, GO) seems equally effective and potentially curative, although evidence in this category is still based on small patient numbers (Burnett *et al*, 2015; Iland *et al*, 2015).

In this review article, we will critically discuss the results of large clinical trials in front-line APL therapy in adults, focusing in particular on recent randomized studies comparing ATRA and chemotherapy *versus* ATRA-ATO. In addition, we will briefly discuss salvage treatment and the evolving role of stem cell transplantation (SCT). Finally, for both newly diagnosed and relapsed disease, we will identify unmet needs

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in treatment and controversial areas that could be the subject of future clinical investigation.

Relevance of early diagnosis and initial management

Acute promyelocytic leukaemia is a medical emergency requiring prompt diagnosis and management. In fact, as we will discuss below, early death mostly due to severe haemorrhage still occurs in a high percentage of cases and today represents the main obstacle to final cure of the disease. Given its rarity (0·14 APL cases per 100 000 are diagnosed each year in the EU) (Sant *et al*, 2014) and due to some important aspects specifically related to the management of the disease, it is appropriate that patients are referred to highly experienced centres.

Acute promyelocytic leukaemia is frequently associated at diagnosis with a consumptive coagulopathy resulting in high risk of haemorrhagic death, thrombosis or both (Choudhry & DeLoughery, 2012; Breccia & Lo-Coco, 2014). This is generally characterized at the laboratory level by significant decrease in platelet number and signs of hyperfibrinolysis (low plasma fibrinogen and increased fibrinogen degradation products or D-dimers). Although the precise pathogenesis of the coagulopathy remains unclear, it is well known that it is effectively counteracted by prompt institution of aggressive supportive care and by specific antileukaemic treatment with ATRA. For this reason, current recommendations strongly suggest that ATRA should be initiated in parallel with massive transfusional support (including platelet units and fresh frozen plasma or fibrinogen concentrates) upon morphological or clinical suspicion only and without waiting for genetic confirmatory tests (Milligan *et al*, 2006; Sanz *et al*, 2009; Tallman & Altman, 2009; Seftel *et al*, 2014; NCCN guidelines, 2015). Recent data from the randomized comparison of ATRA-ATO *versus* ATRA-chemotherapy showed that ATRA-ATO results in decreased early death, suggesting that ATO exerts a better counteractive effect on the coagulopathy compared with chemotherapy (Lo-Coco *et al*, 2013; Burnett *et al*, 2015).

Genetic diagnosis through identification of the t(15,17) translocation and/or the *PML/RARA* fusion gene remains mandatory for patient eligibility to be continued on ATRA or ATO-based treatment, because the presence of the oncoprotein will predict responsiveness to these therapies in virtually all patients (Sanz *et al*, 2009). As for transfusion support, there is a consensus among experts on the need to maintain fibrinogen and platelet levels above 1·5 g/l and 30–50 $\times$ 10^9/l, respectively. These blood parameters and coagulation tests should be repeatedly monitored every 6 h, particularly during the initial 10 d of treatment, with special attention to patients at increased risk of haemorrhage (those with hyperleucocytic disease and those showing worsening consumptive coagulopathy). Prophylaxis with steroids is widely used, with the aim at preventing both haemorrhage and differentiation syndrome (DS), while use of antifibrinolytic or heparin is not recommended. Heparin has been used in cases presenting with greater tendency to thrombosis, however its benefits in APL has remained controversial. Table I summarizes consensus and controversial points in supportive treatment including prevention and management of the APL coagulopathy.

Front-line therapy: historical background

The first important success in APL therapy was reported by Bernard *et al* (1973), who obtained high rates of complete remission (CR) (70%) with daunorubicin given as monotherapy. A significant proportion of patients (approximately 30%) receiving such treatment experienced long-term remission, an unprecedented scenario that still today is not observed for any single chemotherapy agent used for other myeloid or lymphoid acute leukaemias. The observations made in France were independently confirmed in Spain and Italy, and extended to idarubicin (Petti *et al*, 1987; Avvisati *et al*, 1990; Sanz *et al*, 1999). Anthracycline-based chemotherapy remains one of the mainstays of APL treatment, being incorporated into several combinatorial protocols with ATRA and ATO plus ATRA. Notwithstanding this, the reasons underlying the exquisite sensitivity of APL to the effects of anthracyclines remain poorly understood, although absence of the multidrug resistance-associated gp170 protein expression on the surface of APL blasts may contribute at least a partial explanation (Paietta, 2003).

With the introduction of ATRA in the late 1980s, it was shown that CR could be obtained through leukaemic cell differentiation and without significant myelosuppression (Huang *et al*, 1988; reviewed in Wang & Chen, 2008). However, responses with ATRA monotherapy were short-lived in almost all patients and treatment was frequently associated with severe DS (initially referred to as ATRA syndrome) (Frankel, 1992). This led several cooperative groups to design combinatorial approaches in which ATRA was used in association with chemotherapy. A randomized comparative study by Fenaux *et al* (1993) demonstrated that simultaneous ATRA and chemotherapy was better than ATRA and chemotherapy given sequentially. The same group and a US Intergroup collaborative study also showed a benefit from adding maintenance therapy including intermittent ATRA after induction and consolidation (Fenaux *et al*, 1999; Tallman *et al*, 2002).

In keeping with their previous observations, the Gruppo Italiano per le Malattie EMatologiche dell'Adulto (GIMEMA) and the Programa Espanol para el Tratamiento de las HEmopatias Malignas del Adulto (PETHEMA) used only an anthracycline (idarubicin) as chemotherapy in addition to simultaneous ATRA for remission induction, followed by chemotherapy consolidation and maintenance therapy (Avvisati *et al*, 1996; Mandelli *et al*, 1997; Sanz *et al*, 1999). The ATRA plus IDArubicin (or AIDA) regimen was replicated

Table I. Consensus and controversial issues in supportive therapy for newly diagnosed APL.

Consensus (European LeukaemiaNet)	Controversial issues
Management of coagulopathy	
• Treatment with ATRA should be started immediately when a diagnosis of APL is suspected without waiting for genetic confirmation • Liberally transfuse with fresh frozen plasma, fibrinogen and/or cryoprecipitate and platelet transfusions to maintain the fibrinogen concentration above 1·0–1·5 g/l and platelet count above 30–50 $\times$ 10^9/l, respectively • The benefit of heparin, tranexamic acid, other anticoagulant or antifibrinolytic therapy remains questionable and these drugs should not be used routinely outside the context of clinical trials	• Sporadic use of activated factor VII has been reported for massive intracranial haemorrhage; no systematic studies are available, and its use may increase risk of thrombosis
Management of hyperleucocytosis (WBC count >10 $\times$ 10^9/l)	
• Chemotherapy should be started without delay, even if the molecular results are still pending • Leucopheresis should be avoided due to risk of precipitating fatal haemorrhage • Prophylactic steroids can be given, as they may reduce the risk of APL differentiation syndrome	• The optimal cytotoxic agent (idarubicin, gemtuzumab ozogamicin, hydroxycarbamide) remains controversial, especially in the context of chemotherapy-free protocols
Management of APL differentiation syndrome	
• Steroids (10 mg dexamethasone i.v. bd) should be started immediately at the earliest clinical suspicion of incipient APL differentiation syndrome. Once the syndrome has resolved, steroids can be discontinued and ATO/ATRA resumed if previously interrupted • Temporary discontinuation of differentiation therapy (ATRA or ATO) is indicated only in case of severe differentiation syndrome	• Optimal steroid type and duration of prophylaxis is still matter of debate • The subset of patients who benefit from DS prophylaxis is still matter of debate

APL, acute promyelocytic leukaemia; ATRA, all-trans retinoic acid; WBC, white blood cell.

worldwide and became one of the most widely used standard treatments for newly diagnosed patients. The PETHEMA studies contributed to the feasibility of treatment de-intensification with omission of non-anthracycline agents from consolidation and, together with the GIMEMA results, formed the basis for a meta-analysis and a joint collaboration that ultimately led to a proposal for relapse risk assessment. The so-called Sanz risk score, essentially based on WBC count at diagnosis, allowed further refinement of front-line APL therapy through upfront risk assessment and the use of risk-adapted ATRA and chemotherapy (Sanz *et al*, 2000).

Results with risk-adapted ATRA and chemotherapy in newly diagnosed patients

The first PETHEMA trial that used a risk-adapted strategy, LPA99, evaluated consolidation therapy with ATRA plus 3 chemotherapy courses based on intensified idarubicin doses for patients with intermediate- and high-risk APL. Compared with the previous LPA96 trial, the addition of ATRA and intensified chemotherapy significantly reduced the 3-year cumulative incidence of relapse (CIR; 9% vs. 20%, respectively; $P = 0{\cdot}004$) and significantly improved disease-free survival (DFS; $P = 0{\cdot}002$) and overall survival (OS; $P = 0{\cdot}02$) (Sanz *et al*, 2004). The GIMEMA AIDA-2000 risk-adapted trial used cytarabine added to the classic anthracycline-based consolidation chemotherapy for high-risk patients and introduced, like the PETHEMA, ATRA during consolidation cycles for patients of all risk categories. Compared with the previous AIDA-0493 experience, in the AIDA-2000 trial, the 6-year OS and CIR rates for all patients were 78·1% vs. 87·4% ($P = 0{\cdot}001$) and 27·7% vs. 10·7% ($P < 0{\cdot}0001$), respectively. Significantly lower CIR rates for patients in the AIDA-2000 were most evident in the high-risk group (49·7% vs. 9·3%, $P < 0{\cdot}0001$) (Lo-Coco *et al*, 2010). The dramatic reduction in relapse rate obtained in high-risk patients with the addition of cytarabine and ATRA in consolidation was also reported by the PETHEMA LPA-2005 protocol, with a 3-year relapse rate of 11%, compared with 26% in the previous LPA-99 trial ($P = 0{\cdot}03$). The LPA2005 study also investigated a dose reduction of consolidation chemotherapy for low and intermediate-risk patients, together with the addition of ATRA to consolidation therapy. This strategy in non-high risk patients did not produce a survival advantage compared with the previous study, but significantly reduced haematological toxicity and hospitalization in this subset of patients (Sanz *et al*, 2008).

The benefit of a risk-adapted approach generally employing reduced intensity chemotherapy for low-risk patients was confirmed in parallel by several large multicentre studies,

including those conducted in several countries worldwide (Adès *et al*, 2006; Burnett *et al*, 2013; Asou *et al*, 2007; reviewed in Sanz & Lo-Coco, 2011). Overall, these studies concordantly indicated the feasibility and convenience of treatment de-escalation in APL.

Open issues with ATRA and chemotherapy

Several aspects have been the subject of intensive investigation in the setting of ATRA and chemotherapy. The role of cytarabine in induction chemotherapy regimens for front-line therapy of APL has been explored in two prospective European randomized trials that compared ATRA plus anthracycline-based induction combined or not with cytarabine. Although no difference in CR rates was demonstrated in either study, the French-Swiss- Belgian cooperative group showed an increased risk of relapse when omitting cytarabine from induction and consolidation courses (Adès *et al*, 2006). On the other hand, the British Medical Research Council study (MRC AML15 trial) reported a slight increase in number of deaths in remission when cytarabine was administered, however this did not translate in significant differences in survival rates (Burnett *et al*, 2013). While the use of cytarabine for induction has been questioned, there is greater consensus on the benefit from using this agent during consolidation in the high-risk setting.

No studies have directly compared the type of anthracycline used for induction and consolidation, although a recent matched-pair analysis comparing idarubicin and daurorubicin showed no significant difference in antileukaemic effect (Sanz *et al*, 2015).

Another controversial issue relates to the role of central nervous system (CNS) prophylaxis. In fact, the subset of patients who would benefit from CNS prophylaxis is still debated with some investigators omitting it in all patient categories and others recommending it only for high-risk patients (Sanz *et al*, 2009). In addition, the Spanish PETHEMA reported an increased incidence of CNS relapse in patients experiencing CNS bleeding at presentation or during induction. Therefore, these latter cases could be considered for CNS prophylaxis, in all instances however to be carried out at the end of induction (Montesinos *et al*, 2009).

As for maintenance therapy, the survival benefit produced by the addition of maintenance after ATRA plus chemotherapy induction and consolidation has been explored in randomized studies with controversial results. A randomized study conducted in France reported a survival benefit in terms of OS for patients receiving maintenance therapy based either on low-dose chemotherapy, ATRA or concurrent ATRA and chemotherapy, particularly for those who received combined low-dose chemotherapy and intermittent ATRA (Fenaux *et al*, 1999). A large US North Intergroup randomized trial confirmed the survival benefit in both OS and DFS for patients receiving ATRA maintenance after obtaining CR with ATRA plus chemotherapy regimens (Tallman *et al*, 2002). A subsequent GIMEMA trial, randomizing ATRA alone *versus* ATRA plus low-dose chemotherapy *versus* only low-dose chemotherapy *versus* no maintenance therapy, was unable to demonstrate a significant benefit of maintenance therapy in patients treated with the AIDA0493 protocol (Avvisati *et al*, 2011). As an important difference compared with the aforementioned studies, it should be noted that in the Italian study only patients achieving molecular complete remission (mCR) were randomized for maintenance. By convention, mCR is defined as the achievement of polymerase chain reaction (PCR) negativity in bone marrow at the end of consolidation using a test with sensitivity of 1 in 10^3/10^4 (Sanz *et al*, 2009). In keeping with the GIMEMA results, another randomized multicentre trial conducted in Japan by the Japan Adult Leukaemia Study Group (JALSG) reported that intensified maintenance chemotherapy did not improve DFS in patients in mCR after three courses of intensive consolidation therapy (Asou *et al*, 2007).

Alternative approaches for maintenance therapy have been recently investigated. A JALSG trial explored the efficacy of the synthetic retinoid tamibarotene (previously referred to as Am80) as maintenance therapy in newly diagnosed patients, comparing this strategy with ATRA. No difference was detected between the two options in terms of survival, however a trend for improved efficacy was observed for tamibarotene in high-risk patients (Shinagawa *et al*, 2014).

In Table II, we summarize the main consensus and controversial issues in the context of APL treated with conventional ATRA plus chemotherapy regimens.

ATO-based regimens as front-line therapy

Arsenic trioxide was first employed in APL in the early 1990s, and showed high anti-leukaemic efficacy as single agent in patients relapsing after ATRA plus chemotherapy front-line regimens. High CR rates were associated with mild toxicity, particularly in terms of myelosuppression and QTc prolongation (Ohnishi *et al*, 2000; Lengfelder *et al*, 2012). Given the encouraging results in relapsed disease, ATO was soon investigated as part of front-line regimens in APL, both as single agent or in combination with ATRA and/or chemotherapy.

Single-agent ATO front-line therapy has been tested in two prospective non-randomized trials in India and Iran. In both studies ATO was administered as the sole therapy for remission induction and consolidation/maintenance therapy. At 60 months of follow-up, the 5-year OS, event-free survival (EFS) and DFS in the Indian study were 74·2%, 69% and 80%, respectively (Mathews *et al*, 2010). Similar results were reported by Iranian investigators with 5-year DFS and OS rates of 66·7% and 64·4% in the longer follow-up (Ghavamzadeh *et al*, 2011).

In vitro and *in vivo* studies demonstrated a potent synergistic effect of ATRA and ATO. At the molecular level, ATRA and ATO were both shown to induce modulation and/or

Table II. Consensus and controversial issues in frontline treatment with ATRA and chemotherapy.

Consensus (European LeukaemiaNet)	Controversial issues
Induction therapy	
• Induction therapy should consist of the administration of concomitant ATRA and anthracycline-based chemotherapy • Standard induction therapy should not be modified based on the presence of leukaemia cell characteristics that have variably been considered to predict a poorer prognosis (e.g. secondary chromosomal abnormalities, *FLT3* mutations, CD56 expression, and BCR3 PML-RARA isoform) • Treatment with ATRA should be continued until achievement of CR, which occurs in virtually all patients following conventional ATRA + anthracycline induction schedules • Clinicians should refrain from making therapeutic modifications on the basis of incomplete blast maturation (differentiation) detected up to 50 d or more after the start of treatment by morphology, cytogenetics or molecular assessment	• Probably unnecessary the addition of cytarabine to anthracyclines and ATRA for induction
Consolidation therapy	

• Two or 3 courses of anthracycline-based chemotherapy are considered the standard approach for consolidation therapy
• The addition of ATRA to chemotherapy in consolidation provides clinical benefit
• Consolidation for high-risk patients younger than 60 years with WBC counts higher than 10×10^9/l should include at least one cycle of intermediate or high-dose cytarabine
• ATO in consolidation should at present be restricted to investigation within clinical trials or to patients considered unfit for conventional chemotherapy
• Molecular remission in the bone marrow should be assessed at completion of consolidation by RT-PCR assay with sensitivity of 1 in 10^3–10^4
• Patients with confirmed molecular persistence should be considered for allogeneic SCT
	• The subset of patients who benefit from CNS prophylaxis is still matter of debate:
	  • High-risk patients
	  • Patients who had CNS bleeding at presentation or during induction

Management after consolidation	
• Maintenance therapy should be used for patients who have received an induction and consolidation treatment regimen wherein maintenance has shown a clinical benefit • Because early treatment intervention in patients with evidence of MRD affords a better outcome than treatment in full-blown relapse, MRD monitoring of bone marrow should be offered for up to 3 years after completion of consolidation • Bone marrow generally affords greater sensitivity for detection of MRD than blood and allows better MRD monitoring to guide therapy • For patients testing PCR positive at any stage following completion of consolidation, it is recommended that a bone marrow is repeated for MRD assessment within 2 weeks and that samples are sent to a reference laboratory for independent confirmation	• The benefit of maintenance therapy for patients achieving mCR has been questioned • The use of prolonged low-dose chemotherapy may contribute to development of secondary leukaemias • Monitoring may not be cost-effective for those patients with low relapse risk

ATRA, all-trans retinoic acid; ATO, arsenic trioxide; CR, complete remission; mCR, molecular complete remission; WBC, white blood cell; RT-PCR, reverse transcription polymerase chain reaction; SCT, stem cell transplantation; MRD, minimal residual disease; CNS, central nervous system.

degradation of the PML/RARA oncoprotein through direct binding to distinct PML/RARA moieties (Wang & Chen, 2008; de Thé & Chen, 2010; de Thé *et al*, 2012). This potent synergistic effect was documented in clinical studies. In 2004, Chinese investigators from the Shanghai Institute of Haematology published the results of a prospective study that randomized patients to receive ATRA, ATO or the combination of the two agents for remission induction therapy, followed by chemotherapy-based consolidation (Shen *et al*, 2004). ATRA plus ATO produced a faster CR achievement, a more

profound reduction of *PML/RARA* transcripts, and a lower relapse rate when compared with ATRA or ATO as single agents (Shen *et al*, 2004).

Strategies combining ATO plus ATRA ± chemotherapy were investigated by several groups worldwide. A chemotherapy-free approach with ATO plus ATRA was tested in a pilot study by investigators at the MD Anderson Cancer Center (MDACC) for low-intermediate risk APL, with the addition of a single dose of GO at 9 mg/m^2 on the first day of induction therapy for high-risk patients (Estey *et al*, 2006). In the final extended series of 82 patients, 65 were treated with ATO starting on day 10 of induction therapy and the rest with ATO started concomitantly with ATRA on the first day of therapy (Ravandi *et al*, 2009). After induction, all patients received 4 consolidation cycles with ATRA and ATO. Overall, the response rate after induction was 92%, with seven early deaths occurring within the first 24 d after inclusion in the study. With a median follow-up of 24 months, three patients relapsed and three died in CR, all from a second malignancy. The estimated 3-year survival rate was 85%.

A US Intergroup study investigated the benefit of ATO added to ATRA and chemotherapy consolidation (Powell *et al*, 2010). Patients were randomized to receive either a standard induction regimen consisting of ATRA, cytarabine and daunorubicin, followed by two courses of consolidation therapy with ATRA and daunorubicin, or to the same induction and consolidation regimen with two 25-d additional courses of ATO administered after induction. Three-year EFS was significantly better for patients receiving ATO consolidation compared with standard therapy (80% vs. 63%, $P < 0{\cdot}0001$), as was 3-year DFS. ATO as part of consolidation therapy was employed in another US prospective, non-randomized study administering standard ATRA and daunorubicin for induction therapy followed by one consolidation cycle with combined ATO and cytarabine and daunorubicin (Gore *et al*, 2010). A total of 45 patients were enrolled in this study and, after a median follow-up of 2·7 years, estimated DFS and OS were 90% and 88%, respectively. Together, these studies further indicated the possibility of reducing the need for chemotherapy when ATO was included as part of front-line treatment.

In 2012, the Australasian Leukaemia and Lymphoma Group published the single arm phase II APML4 study combining ATO, ATRA and chemotherapy as front-line therapy for APL of all risk categories (Iland *et al*, 2015). Induction therapy consisted of the AIDA schedule with the addition of ATO at 0·15 mg/kg from day 9 to 36. Consolidation consisted of 2 additional cycles of ATRA and ATO without chemotherapy, followed by maintenance with low-dose chemotherapy. The 2-year rate for freedom from relapse was 97·5% and for OS, 93·2%. Compared with historical controls (APML3 protocol) based on standard ATRA plus chemotherapy approach, patients in the APML4 had a significantly improved freedom from relapse and failure-free survival. The results of the main ATO-based studies in front-line APL, with the exception of the two randomized ATRA + ATO *versus* ATRA-chemotherapy comparative trials, which are reported separately, are shown in Table III.

ATRA + ATO *versus* ATRA + chemotherapy randomized studies

Two large multicentre studies compared the ATRA-ATO combination *versus* the standard ATRA-chemotherapy

Table III. Results with ATO (±ATRA ± chemotherapy) in front-line treatment.

Study	Patients (*n*)	Therapy	CR, %	mCR, %	Relapse, %	OS, %	DFS, %
Shen *et al* (2004)	61	ATRA alone	95	NR	26	91·7	70
		ATO alone	90		11	(5 years)	88
		ATRA + ATO	95·2		–		100
Ravandi *et al* (2009)	82	ATO + ATRA (+GO)	92	92	4	85	ND
						(3 years)	
Mathews *et al* (2010)	72	ATO alone	86	69·7	NR	74·2	80
						(5 years)	(5 years)
Gore *et al* (2010)	45	Standard CHT + ATO consolidation	91	97	2·2	88	90
Powell *et al* (2010)	481	Standard CHT	90	NR	NR	86	70
		Standard CHT + 2 ATO cycles	90	NR	NR	81	90
						(3 years)	(3 years)
Ghavamzadeh *et al* (2011)	94	ATO alone	86·3	92	25·3	64·4	66·7
						(5 years)	(5 years)
Zhu *et al* (2013)	242	Oral arsenic	99·1	100	0·8	99·1	98·1
		i.v. ATO	97·4	100	0·8	96·6	95·5
						(3 years)	(2 years)
Iland *et al* (2015)	124	ATO + CHT + ATRA	95	100	1·7	94	95
						(4·2 years)	(4·2 years)

CR, complete remission; mCR, molecular complete remission; OS, overall survival; DFS, disease-free survival; ATRA, all-trans retinoic acid; ATO, arsenic trioxide; GO, gemtuzumab ozogamicin; CHT, chemotherapy; NR, not reported; ND, not done.

approach in newly diagnosed patients. The APL0406 trial conducted in Italy and Germany by the GIMEMA, AML Study Group (AMLSG) and Study Alliance Leukaemia (SAL) cooperative groups, randomized patients with low/intermediate risk APL to receive ATRA plus ATO or the standard ATRA and chemotherapy (AIDA) (Lo-Coco *et al*, 2013). The experimental arm was derived from the MDACC study, with ATO and ATRA given concomitantly as remission induction therapy starting from day 1, followed by 4 consolidation cycles with intermittent ATO (4 weeks on/4 weeks off) and ATRA (2 weeks on/2 weeks off) and with no maintenance therapy. The study results, reported in 2013, showed that ATO-ATRA was superior in terms of both EFS and OS compared with AIDA (2-year EFS: 97% vs. 86%, $P = 0{\cdot}02$; 2-year OS: 99% vs. 91%; $P = 0{\cdot}02$). As expected, the chemotherapy-free approach was associated with considerably less haematological toxicity. Patients receiving ATRA-ATO experienced frequent liver enzyme increase and QT prolongation, which were successfully managed with temporary discontinuation and/or dose adjustment. A recent update of the study on an extended final series of 276 patients showed increasingly better results for patients in the ATRA-ATO arm (2-year EFS 98% vs. 84·9%, $P = 0{\cdot}0002$), 2-year OS 99·1% vs. 94·4%, $P = 0{\cdot}01$). The analysis on the extended series also showed a significantly lower CIR in the ATRA plus ATO group compared with the AIDA cohort (1·1% and 9·4%, respectively; $P = 0{\cdot}005$) suggesting greater efficacy of this approach (Platzbecker *et al*, 2014).

The UK National Cancer Research Institute (NCRI) group recently reported the randomized trial AML17, which compared a chemotherapy-free ATO plus ATRA combination with the standard AIDA regimen (Burnett *et al*, 2015). The study included 57 high-risk out of a total of 235 enrolled patients. As in the MDACC study (Ravandi *et al*, 2009), there was a provision for high-risk patients to receive a single infusion of GO (at 6 mg/m^2) during the first 4 d of induction therapy. At variance from the GIMEMA-AMLSG-SAL study, the NCRI adopted a different ATO schedule (0·3 mg/kg on days 1–5 of each course and then at 0·25 mg/kg twice weekly in weeks 2–8 of course 1 and weeks 2–4 of courses 2–5); moreover, unlike the Italian-German trial, the control arm in the NCRI study contained no maintenance. CR after induction therapy was achieved in 89% and 94% patients in the ATRA-chemotherapy and ATRA-ATO arms respectively, with a 30-d mortality of 6% and 4%, respectively. The 4-year molecular recurrence-free survival was 70% in patients receiving ATRA and idarubicin and 98% in those treated with ATO and ATRA ($P \leq 0{\cdot}0001$). Similarly, 4-year cumulative incidence of molecular relapse was higher in the ATRA and idarubicin arm compared with ATO + ATRA arm (18% vs. 1%; $P = 0{\cdot}0007$). The 4-year OS in the NCRI study was comparable between the ATO and chemotherapy group (93% vs. 89%; $P = 0{\cdot}25$). The study reported similar types of toxicities as in the GIMEMA APL0406 study for patients in the ATO group in terms of DS and cardiac side effects, with a lower incidence of grade 3–4 hepatic toxicity. Interestingly, compared to their previous AML15 trial, which included maintenance, the rate of therapy-related myeloid neoplasms (t-MN) in the AML17 dropped from 9/285 to 1/119 considering patients receiving chemotherapy. To the best of our knowledge, no cases of t-MN have been reported so far in major ATO-based studies (Mathews *et al*, 2010; Powell *et al*, 2010; Lo-Coco *et al*, 2013; Burnett *et al*, 2015; Iland *et al*, 2015).

Taken together, the results of the two studies provide strong evidence in favour of the chemotherapy-free ATRA-ATO and point to this strategy as a new standard of care for low-intermediate risk patients. The main findings of the two randomized trials are summarized in Table IV.

Open issues in front-line regimens including ATO

The results obtained with ATO-ATRA in low-intermediate risk patients by the APL0406 (Lo-Coco *et al*, 2013) led the NCCN (NCCN, 2015) and a Canadian expert panel (Seftel *et al*, 2014) to indicate the chemo-free regimen as a new standard in this setting. This recommendation for low-intermediate risk patients is now reinforced with results along the same lines provided by the independent randomized study of the NCRI (Burnett *et al*, 2015). Open issues remaining in this area include the type of ATO schedule to be administered and the possibility of eventually switching to oral

Table IV. Randomized, prospective studies comparing ATRA + CHT *versus* ATRA + ATO.

Study	Patients (*n*)	Median age [years] (range)	Treatment	CR (%)	EFS (%)	OS (%)	CIR (%)	DFS (%)	Median follow-up
Lo-Coco *et al* (2013) (APL0406)	276	46 (18·7–70·2)	ATRA + ATO	100	98	99·1	1·1	98	36 months
			versus	97	84·9	94·4	9·4	87·9	(1–75)
			ATRA + CHT						
Burnett *et al* (2015) (AML17)	235	47 (16–77)	ATRA + ATO	94	91	93	1	NR	30·5 months
			versus	89	70	89	18		(3–41·2)
			ATRA + CHT						

CR, complete remission; EFS, event-free survival; OS, overall survival; CIR, cumulative incidence of relapse; DFS, disease-free survival; APL0406, acute promyelocytic leukaemia 0406 trial; AML17, acute myeloid leukaemia 17 trial; ATRA, all-trans retinoic acid; ATO, arsenic trioxide; GO, gemtuzumab ozogamicin; CHT, chemotherapy; NR, not reported.

arsenic, assuming that this formulation might be available in the near future. While preliminary evidence obtained from China suggests that oral arsenic plus ATRA is equally effective and safe in low-intermediate APL as i.v ATO plus ATRA (Zhu & Huang, 2014), the results of an on-going randomized comparison are awaited.

As for high-risk disease, preliminary evidence from trials combining ATRA-ATO with chemotherapy (idarubicin in the Australasian APML4 or GO in the AML17) indicate high efficacy of ATO in this subset of patients and suggest that the triple association (so-called 'triple A' for ATRA-ATO-Anthracycline) may be curative in high-risk patients as well, minimizing the necessary amount of chemotherapy (Burnett *et al*, 2015; Iland *et al*, 2015). However, the type and dose of initial chemotherapy needed during induction in association with ATRA-ATO are unclear. In addition, while GO was repeatedly shown to be highly effective in this setting (Ravandi *et al*, 2012), this agent has been withdrawn from the market and is not presently available for clinical use in Europe and the US. Given the uncertainties and scarce data from randomized studies available in high-risk APL, a multicentre study is presently being launched as a European Intergroup collaboration to compare ATRA-ATO plus 2 doses of idarubicin (given only for induction) *versus* the standard AIDA (including cytarabine in consolidation).

Another area still open to debate and investigation is the management of complications of ATO therapy. Among these, QTc prolongation is one of the most common and has recently been the subject of a single-centre US study, which aimed at identifying the optimal correction formula to be employed in QTc calculation (Roboz *et al*, 2014). The study reported that currently used ATO schedules are devoid of clinically significant cardiac arrhythmias and that overestimation of the QT prolongation may result from inappropriate correction formulas (such as Bazett). As a consequence, a recommendation was made in this study to use appropriate correction of the QT and to increase the threshold for ATO temporary withdrawal in clinical practice at 500 ms instead of the current 460–470 ms (Roboz *et al*, 2014).

Hyperleucocytosis developing after the beginning of therapy is another side effect frequently seen in patients with non-high risk APL receiving the chemo-free ATRA-ATO regimen. It is very important that isolated hyperleucocytosis is distinguished from DS as the latter requires a distinct therapeutic approach (see above). In the Italian-German APL0406 trial, hydroxycarbamide (also termed hydroxyurea) alone was sufficient to control increased WBC count during induction in all patients experiencing this complication, while GO (one dose at 6 mg/m^2) was used for the few low-intermediate patients developing hyperleucocytosis in the UK NCRI trial.

Neurological toxicity mainly consisting of peripheral neuropathy has been reported in studies employing ATO. Usually, this mild side effect was managed with temporary discontinuation. Scarce data are available on neurotoxic effects of ATO in the long-term.

One important unsolved issue related to ATO-based regimens is whether CNS prophylaxis is needed or not in this therapeutic context. In fact, specific pharmacodynamic studies indicated that approximately one-third of ATO crosses the blood-brain barrier (Kiguchi *et al*, 2010), which could suggest that a sufficient amount of drug is available on site to prevent disease recurrence. Long-term outcome results with ATO are awaited to better clarify this issue.

Finally, accessibility to ATO for front-line therapy is a major problem because the drug is currently only approved for treatment of disease relapse in the US and Europe. Furthermore, the commercially available drug is extremely expensive and this further limits patient access to the new treatment. Given the available evidence on its benefit, it is desirable that labelling extension of ATO could be soon approved in order to facilitate patient access to the drug.

The unsolved problem of early death

The impressive improvement in APL outcomes and the current long-term cure rates exceeding 90%, reported in modern clinical trials, have been recently challenged by registry-based studies exploring APL outcomes in the real world. Four population-based studies from Sweden, Canada and US have highlighted the issue of early mortality in APL, whose rate is reduced to very low patient fractions (approximately 5%) in clinical trials after the introduction of ATRA- and chemotherapy- based protocols. The Swedish investigators first reported the possible discordance between clinical trials and data from the real world on early mortality rates (Lehmann *et al*, 2011). Of 105 APL patients diagnosed between 1997 and 2006, 30 (29%) died within 30 d of diagnosis, mostly due to fatal haemorrhagic events. Data from the US Surveillance, Epidemiology, and End Results registry on a larger series of 1400 APL patients diagnosed between 1992 and 2007 confirmed high early death rates of 17·3%, with no significant change over time (Park *et al*, 2011). In line with the above reports, a Canadian registry study reported an overall early mortality rate of 21% in a population of 399 APL patients diagnosed between 1993 and 2007 (Paulson *et al*, 2014). All studies consistently reported older age, high WBC counts and poor performance status as predictive factors for early mortality. A high percentage of early deaths was recorded in patients who were not started on ATRA (35% in the Swedish study) and early mortality rate was lower when patients were treated in specialized leukaemia Institutions (Paulson *et al*, 2014). A recent single centre study from Stanford University reported an early mortality rate reaching 30% for APL patients diagnosed and treated from 1997, with no delay observed in diagnosis or ATRA administration (McClellan *et al*, 2012). In another single-centre study from Italy, patients with life-threatening haemorrhages before starting therapy had delayed diagnosis due to initial hospitalization in non-specialized, primary care

institutions with no experience in treatment of leukaemia (Breccia *et al*, 2010).

These data indicate that early mortality still represents a challenge in APL therapy and that it is currently an underestimated phenomenon in clinical trials due to exclusion from studies for old age or poor performance. In addition, the above studies indicate the need for greater educational effort at primary care and emergency centres in order to improve early diagnosis and patient referral to specialized centres.

Current therapy for relapsed patients and role of SCT

Current literature on the treatment of relapsed APL is only available for patients relapsing after ATRA and chemotherapy. Given the more recent use of ATO and the improved outcome obtained with this agent, very few studies have reported results of small series of patients in the setting of relapse after ATO-based treatment. It is likely that the current scenario of APL relapse will change in the near future, and the clinical and biological features of post-ATO relapses, together with their optimal management, will be the subject of present and future investigation.

About 20% of patients have been reported to relapse after modern, risk-adapted ATRA and chemotherapy regimens (Lengfelder *et al*, 2005). Three studies showed the clinical benefit of early identification of disease recurrence and preemptive therapy at the time of molecular relapse (Grimwade, 1999; Lo-Coco *et al*, 1999; Esteve *et al*, 2007). This is conventionally defined as two consecutive reverse transcription-PCR (or real-time quantitative-PCR) positive tests in marrow samples collected 2–4 weeks apart after front-line induction and consolidation. The quantitative RQ-PCR assay offers the possibility of measuring the kinetics and trend of *PML/RARA* transcripts. In historical comparisons, early therapeutic intervention increased the probability of overall survival as compared with patients who received salvage treatment at the time of haematological relapse (Grimwade, 1999; Lo-Coco *et al*, 1999; Esteve *et al*, 2007). Treatment of molecular relapse was associated with some benefits, such as a better-tolerated treatment, without need of hospitalization and without recorded early death and DS. Given the improvements in front-line therapy discussed above and the very low risk of relapse with novel regimens, the value of extensive molecular monitoring beyond achievement of molecular remission may be questioned, at least in low-risk disease.

In 2009, an expert panel on behalf of the European LeukaemiaNet published recommendations for management of relapsed APL based on evidence reported in the literature. Two cycles of ATO ± ATRA were considered the best option for patients relapsing after ATRA and chemotherapy. In patients achieving a second mCR, the suggested options were intensification with autologous SCT or, alternatively, prolonged ATRA-ATO. In the absence of a randomized comparison, the choice between these two options should rely on individual assessment, taking into consideration patient age and performance status and the duration of first CR. Allogeneic SCT was recommended for patients who fail to achieve a second mCR after two ATO cycles or in those who relapse after a short-lived (<1 year) first CR (Sanz *et al*, 2009). NCCN 2015 guidelines recommend the use of an ATO-containing regimen in relapsed APL patients not previously exposed to ATO either in late relapse (>6 months) or in early relapse (<6 months) after an ATO/anthracycline containing regimen. For patients previously exposed to ATO-ATRA (without anthracycline), standard ATRA-chemotherapy regimens are recommended with the addition of ATO, 0·15 mg/kg/d. Patients who remain PCR positive after two cycles of treatment who cannot receive an allogeneic SCT should be proposed for investigational trials (Seftel *et al*, 2014; NCCN guidelines, version 1.2015).

The first experiences with ATO as salvage treatment in APL were reported in China (Shen *et al*, 1997) and North America. The US Intergroup study, whose results led to approval of ATO as salvage therapy by the US Food and Drug Administration and European Medicines Agency, showed a CR rate of 85% in 40 patients treated with ATO as single agent, with an estimated 18-month survival of 66% (Soignet *et al*, 2001). In a literature review, Lengfelder *et al* (2012) reported more than 300 patients treated at relapse with ATO between 1997 and 2011, usually with 1–2 monthly re-induction schedules of 0·15 mg/kg/d given i.v. and variable post-induction therapies, with 60 patients receiving autologous or allogeneic SCT. The study reported a CR rate of 86%, a mCR rate of 52% after the first cycle which increased to up to 80% after the second cycle, with 7% early death mortality and resistance rates, and estimated 2-year OS ranging from 50% to 81% (Lengfelder *et al*, 2012). A meta-analysis showed that the ATRA plus ATO combination increased the CR rate post-consolidation (70% vs. 39% with ATO alone) and the 2-year DFS (85% vs. 64%), without increasing early death rate (Wang *et al*, 2011). Two more recent studies again reported the efficacy of ATO in first relapse: Lou *et al* (2014) reported 64 patients treated with ATO in first relapse (12 molecular and 52 overt haematological relapse). At a median follow-up of 27 months, 3-year relapse-free survival (RFS) and OS were 81·5% and 100% in the molecular relapse group, compared with 57% and 72% in the haematological relapse group, respectively. Autologous or allogeneic SCT was recommended for patients under 60 years.

A registry study of the European LeukaemiaNet recently reported on 155 patients treated with ATO in first relapse: 104 received the drug for haematological relapse, 40 for molecular relapse and 11 for extramedullary relapse. A higher rate of APL DS (27% vs. 0%) and infections (43% vs. 10%) was recorded in patients treated in haematological relapse as compared with molecular relapse. These data show the significant advantage of stringent molecular follow-up in order to anticipate treatment at the time of molecular relapse, both

for chemo-free as for chemotherapy-based regimens. No consensus has been reached on the duration of molecular follow-up in the setting of APL relapse.

The choice of post-consolidation approaches including autologous allogeneic SCT or other treatments remains debated due to the lack of randomized studies (Lengfelder *et al*, 2015). The French group retrospectively reviewed and compared autologous *versus* allogeneic transplants in the relapse setting: 7-year RFS and OS were 79·4% and 59·8% for autologous and 92·3% and 51·8% for allogeneic transplanted patients, but with increased mortality rate in the allogeneic setting (de Botton *et al*, 2005). An EBMT survey in a group of 195 patients reported similar results with 51% 5-year EFS and 16% treatment-related mortality (Sanz *et al*, 2007).

A multicentre Italian retrospective experience reported 31 patients receiving allo-SCT for CR2 or CR3 with 5-year OS of 45% and TRM of 19%: probability of survival depended on CR number and PCR status at time of SCT (Ramadan *et al*, 2012). In another study, 37 relapsed patients treated with ATO-ATRA were randomized to continue with the same regimen or autologous consolidation after achievement of a second remission: OS and EFS were higher in patients who received autologous SCT (Thirugnanam *et al*, 2009). In a single-centre study, 13 patients were autografted in second mCR after chemotherapy and ATRA for reinduction: after a median follow-up of 25 months, 10 patients were alive in mCR (Ferrara *et al*, 2010). A phase 2 prospective study from Japan assessed autologous SCT with PCR-negative harvest after ATO was used for re-induction and consolidation in 23 out of 35 patients who were fit for the procedure: in the whole cohort, they reported and OS of 65% and EFS 77% with a survival curve that reached a stable plateau after 2 years (Yanada *et al*, 2013).

In summary, autologous SCT appears to be a suitable option for younger patients in second mCR capable of receiving high dose chemotherapy as conditioning regimen. However, this option may be questioned for patients relapsing after very prolonged first CR (>2 years) in which continued ATRA and ATO (for up to 5–6 cycles) without SCT might be curative (Breccia *et al*, 2011). Allogeneic SCT should be restricted to patients not achieving mCR after two cycles of re-induction therapy.

Central nervous system prophylaxis is usually recommended at relapse using the same precautions in case of haematological relapse, i.e. avoiding lumbar puncture in cases with overt relapse and postponing the procedure before consolidation.

Current new therapeutic strategies

Oral arsenic formulations have been reported to be effective in relapsed and newly diagnosed APL (Au *et al*, 2003; Zhu *et al*, 2013). Oral tetra-arsenic tetra sulphide (indigo realgar) has been recently tested as frontline treatment and compared with the conventional i.v ATO in a non-inferiority study. A total of 242 patients were randomly assigned to oral or i.v. arsenic plus ATRA for induction and three consolidation courses, and then stratified for oral or i.v. ATO plus ATRA maintenance according to the induction arm. After a median follow-up of 39 months, no significant differences were observed in CR rates or 3-year OS (99·1% vs. 96·6%) (Zhu *et al*, 2013). Oral arsenic also showed a safety profile comparable to i.v. ATO in the same study, with no differences in the rate of non-haematological side effects, and similar incidence of grade 3–4 liver adverse events (Zhu *et al*, 2013). A pilot study was conducted by the same group in 20 non-high risk patients treated with oral ATO and ATRA, without chemotherapy (Zhu & Huang, 2014). Post-remission therapy included oral ATO on a 4 weeks on/4 weeks off schedule and ATRA for 7 months. All patients achieved morphological CR after the first month of therapy and mCR of 100% at 6 months. At a median follow-up of 14 months, no relapses had occurred and half of patients were treated on an outpatient basis (Zhu & Huang, 2014).

The synthetic retinoic AM80 or tamibarotene has been initially tested in relapsed/refractory APL. This agent showed greater retinoic acid receptor binding capacity *in vitro*, low binding affinity to cellular retinoic acid binding protein 1 and increased differentiation induction potential (Ohnishi, 2007). In a small study including 24 evaluable patients, 14 (58%) achieved CR and the major side effects were hypercholesterolemia and hypertriglyceridemia (Tobita *et al*, 1997). Recently, a randomized Japanese study tested the same agent as maintenance therapy in comparison to ATRA. No significant differences were reported in the long-term follow-up analysis, however increased efficacy for tamibarotene was observed in high-risk patients (Shinagawa *et al*, 2014). Tamibarotene was also tested at 6 mg/m^2 for induction and consolidation in a phase II trial in APL patients refractory or relapsed after treatment with ATO and ATRA. Overall response rate was 64% with 21% mCR. Relapses were frequent after a median of 4·6 months (Sanford *et al*, 2015). These data suggest activity efficacy of tamibarotene in advanced disease; its use in association with ATO will probably be explored in the near future.

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LC and MB reviewed the literature and wrote a first draft of the paper. FLC identified and designed the review sections and tables and wrote the paper.

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